Developmental differences in diffusion tensor imaging parameters in borderline personality disorder

Antonia S. New a,b,*, David M. Carpenter b, M. Mercedes Perez-Rodriguez a,b, Luis H. Ripoll a,b, Jennifer Avedon b, Uday Patil c, Erin A. Hazlett a,b, Marianne Goodman a,b

a The Mental Illness Research Education and Clinical Center, James J. Peters Veterans Affairs Medical Center, NY, USA
b Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA
c University of Texas Southwestern Medical Center at Dallas, USA

Article history:
Received 27 August 2012
Received in revised form 27 February 2013
Accepted 28 March 2013

Keywords:
Borderline personality disorder
Diffusion tensor imaging
Inferior longitudinal fasciculus
Development
Neuroimaging

ABSTRACT

Background: Borderline personality disorder (BPD) often presents during adolescence. Early detection and intervention decreases its subsequent severity. However, little is known about early predictors and biological underpinnings of BPD. The observed abnormal functional connectivity among brain regions in BPD led to studies of white matter, as the neural substrate of connectivity. However, diffusion tensor imaging (DTI) studies in adult BPD have been inconclusive, and, as yet, there are no published DTI studies in borderline adolescents.

Methods: We conducted DTI tractography in 38 BPD patients (14-adolescents, 24-adults) and 32 healthy controls (13-adolescents, 19-adults).

Results: We found bilateral tract-specific decreased fractional anisotropy (FA) in inferior longitudinal fasciculus (ILF) in BPD adolescents compared to adolescent controls. ILF FA was significantly higher in adolescent controls compared to BPD adolescents, BPD adults and adult controls (Wilks’ $F(3,57) = 3.55, p < 0.02$). Follow-up voxelwise TBSS analysis demonstrated lower FA in BPD adolescents compared to adolescent controls also in uncinate and occipitofrontal fasciculi.

Discussion: FA generally develops along an inverted U-shape curve, increasing through adolescence, and slowly decreasing in adulthood. Our findings suggest that, in adolescent BPD, this normal developmental “peak” in FA, which is seen in healthy controls, is not achieved. This suggests a possible neural substrate for the previously reported OFC-amygdala disconnect in adults with BPD. It raises the possibility that a white matter tract abnormality in BPD present in adolescence may not be appreciable in adulthood, but a functional abnormality in the coordination among brain regions persists. Our finding represents a possible biological marker to identify those at risk for developing BPD.

1. Introduction

Borderline personality disorder (BPD) is a complex and serious mental disorder characterized by emotional dysregulation, poor impulse control and impaired interpersonal relationships (New et al., 2008b) with a substantial risk for completing suicide (Leichsenring et al., 2011). The full manifestations of BPD become evident during adolescence (Goodman et al., 2011), and it is in adolescence when individuals with BPD usually seek treatment (Chanen et al., 2008a). BPD can be diagnosed in adolescents using similar diagnostic instruments to those used in adults (Chanen et al., 2008b). Early detection and intervention in BPD has been shown to decrease symptom severity and improve functioning (Chanen et al., 2008a). However, little is known about early predictors and biological underpinnings of BPD. In the present study, we aimed to fill this gap in knowledge by searching for a biomarker that could help with earlier identification of BPD in young people.

1.1. Neuroimaging findings in adult BPD

The neuroimaging literature in BPD patients is rapidly growing (Mauchnik and Schmahl, 2010; New et al., 2008a), and studies support the hypothesis of a dysfunctional frontolimbic network in BPD, which appears to involve anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC),...
hippocampus, and amygdala. It is believed that alterations in this network are related to the diminished top-down control of affective and aggressive responses (Leichsenring et al., 2011; New et al., 2008b). The most consistent structural imaging finding in adult BPD is a decrease in gray matter volume in ACC (Hazlett et al., 2005; Minzenberg et al., 2008; Tebartz van Elst et al., 2003) and hippocampus (Brambilla et al., 2004; Irlé et al., 2005; Nunes et al., 2009; Zetzschke et al., 2007). Other findings include volume reduction in the left OFC (Tebartz van Elst et al., 2003) and amygdala (Nunes et al., 2009).

One theory as to what might underlie the striking symptoms of emotional lability and hyper-reactivity which characterizes BPD is that the coordinated function among brain areas is abnormal, and in fact, we previously showed a marked functional disconnect between OFC and amygdala in adult BPD (New et al., 2007). This observation led to an examination of white matter in BPD as the neural substrate of connectivity. To date, only three diffusion tensor imaging (DTI) studies have been published in adults with BPD (Grant et al., 2007; Rusch et al., 2010; Rusch et al., 2007). One found decreased fractional anisotropy (FA) in the OFC in women with BPD compared to controls (Grant et al., 2007), although another showed no significant difference in DTI between adults with both BPD and attention-deficit hyperactivity disorder (ADHD) and controls, but did find a correlation between FA and lifetime depressive symptoms (Rusch et al., 2007). The same group recently found impaired inter-hemispheric structural connectivity in BPD subjects with ADHD (Rusch et al., 2010).

### 1.2. Neuroimaging findings in adolescent BPD patients

Structural neuroimaging data in adolescent BPD is limited. One study found volume reduction in left ACC (Whittle et al., 2009), while another found reductions in dorsolateral PFC and OFC, but not ACC (Brunner et al., 2010). Other studies reported right-sided OFC gray matter reduction in adolescent BPD, but not in amygdala or hippocampus (Chanen et al., 2008c). In a sample overlapping with the present sample, we found that adolescents with BPD and MDD had decreased ACC gray matter volume compared to healthy controls (Goodman et al., 2011). There have been no published DTI studies in borderline adolescents to date.

### 1.3. Developmental changes in DTI

While structural imaging provides quantitative information about brain tissue volume, DTI provides information about the white matter tracts connecting brain regions. There are profound developmental changes in white matter, reflected in the outcome measure of DTI most commonly used, Fractional Anisotropy (FA), thought to reflect both myelination and organized directionality of white matter tracts (Madler et al., 2008). The developmental trajectory exhibited in most white matter tracts includes a sharp increase in FA up to the age of 2–3 years, followed by a gradual increase through adolescence and into the mid-third decade (Asato et al., 2010; Bava et al., 2010; Trivedi et al., 2009; Westlye et al., 2010). While FA increases progressively through adolescence, there is a leveling off and slow decrement of FA in adulthood (Hasan et al., 2010).

Little is known about the developmental trajectory of either structural brain imaging or DTI in BPD. Some structural alterations in BPD are observed both in adolescents and adults, while others have only been reported either early or late in the development of the disorder. It has been suggested that volume changes in prefrontal cortex may appear early in BPD, while volume changes in limbic structures might appear later as a function of the course and/or severity of BPD (Brunner et al., 2010; Chanen et al., 2008c). Since there are no published DTI studies in borderline adolescents, the developmental trajectory of white matter tracts in BPD remains unanswered. The present study aims to address this question by comparing DTI findings in two samples of BPD patients (adolescents and adults) and two age- and sex-matched healthy control (HC) samples.

### 2. Methods

#### 2.1. Adolescent samples

Twenty-seven adolescents (14 BPD, 13 HC matched by age and sex) underwent diagnostic and structural brain imaging with DTI. BPD patients met DSM-IV (SCID-II) (First, 1997) and Diagnostic Interview for BPD-revised (DIB-R) criteria for BPD (Zanarini et al., 2002), while controls had no current axis I or II diagnosis as assessed by the SCID-I/P (First, 2002) and SCID-II. The DIB-R was included to ensure that adolescent BPD subjects met a high threshold level for BPD diagnosis. Adolescent BPD patients were recruited from the adolescent psychiatric inpatient service at The Mount Sinai Hospital in New York City, and HC were recruited from the surrounding community by advertisements. All except one adolescent BPD subject also met criteria for current MDD. Adolescents were excluded for 1) history of serious head injury or neurological disorder; 2) schizophrenia, any other psychotic disorder, bipolar disorder type I or pervasive developmental disorder.

#### 2.2. Adult samples

Twenty-four adult BPD patients and 19 adult HC (1 excluded due to MRI artifact) matched by sex and age completed the study. Individuals from 18 to 55 years of age were recruited through local newspaper advertisements and clinical referral. Subjects were excluded for: 1) history of serious head injury or neurological disorder; 2) current alcohol and/or drug abuse or dependence; 3) schizophrenia, any other psychotic disorder or bipolar disorder type I; or 4) current psychiatric medication. Axis I disorders were assessed with the SCID-I/P and Axis II with the SDP-IV (Pfohl et al., 1996). Healthy controls had no personal history of Axis I or II diagnoses.

This study was approved by Mount Sinai’s Institutional Review Board. All adult participants provided written informed consent prior to participation. Assent was obtained for adolescents and written informed consent was obtained from each adolescent subject’s parent or guardian.

#### 2.3. Self report measures

Depressive symptoms were assessed with the Beck Depression Inventory (Beck et al., 1961); trait aggression was measured with the Buss Perry Aggression Questionnaire (BPAQ), a 29-item questionnaire (Buss and Perry, 1992), and the State-Trait Anger Expression Inventory (STAXI) (Spielberger et al., 1983). Affect lability was measured with the Affect Lability Scale (ALS), a 54-item self-report measure in which subjects rate their agreement with statements regarding the tendency of their mood to shift (Harvey et al., 1989). Impulsivity was measured with the Barratt impulsivity scales-11 (BIS) (Barratt, 1965), a 34-item questionnaire that assess motoric (acting without thinking), cognitive (hasty decisions) and nonplanning (failure to plan ahead) impulsiveness. Each item is rated on a 4-point scale ranging from “Rarely/never” to “Almost always/Always” (Patton et al., 1995).

#### 2.4. DTI methods

DTI was acquired on a 3T Allegra MRI scanner (Siemens, Erlangen, Germany) with the following parameters: a pulsed-gradient spin-echo sequence with EPI-acquisition (TR = 4100 ms,
TE = 80 ms, FOV = 21 cm, matrix = 128 × 128, 28 slices, thickness = 3 mm skip 1 mm, b-factor = 1250 s/mm², 12 gradient directions, 5 averages).

DTI-tractography was implemented in Matlab v2009 (The Mathworks) and used the brute-force (Huang et al., 2004), streamline (Mori and Barker, 1999) algorithm with multiple anatomical criteria for each tract to increase the validity of the tractography (Huang et al., 2004). Streamline termination criteria for FA was <0.10 and for inter-voxel deflection was (>45°). To minimize inter-subject variance and maximize reproducibility, all anatomical tracking criteria were defined on a study-specific template that was created with the tract-based spatial statistics package (TBSS) of FSL (FSL, Oxford, www.fmrib.ox.ac.uk/fsl). Tracking criteria were converted from template coordinates to each subject’s DTI image using the transformation determined by the TBSS routine. For a more detailed description of the tractography methods see Carpenter et al. (2008). The anatomical definitions for tracking the genu and splenium of the corpus callosum, bilateral inferior longitudinal fasciculus (ILF), and bilateral cingulum bundle were established previously by Wakana et al. (2007).

The TBSS voxel-wise statistical analysis was also used to further investigate the tractography findings in the ILF in adolescents. The analysis was conducted to answer two questions: 1) Are the differences in FA that were identified using tractography localized to any portion of the ILF? 2) Are the differences in FA unique to the ILF or are they present in other tracts of the temporal lobe, not assessed in our tractography analysis, including the uncinate fasciculus and the occipitofrontal fasciculus. The JHU White-Matter Tractography Atlas provided with FSL was used to limit the TBSS analysis to the ILF, uncinate and occipitofrontal fasciculus. For completeness, the results of a whole brain TBSS analysis are reported. Hypothesis testing was performed with the TFCE (Threshold-Free Cluster Enhancement) option in randomize of FSL and significance was determined by p < 0.05 family-wise error corrected for multiple comparisons.

For comparison of the interaction of diagnostic group and age cohort, we performed a mixed factorial repeated measures analysis of variance on FA in an age cohort (adolescent, adult) × group (BPD, HC) × sex (male, female) × tract analysis (forceps major, forceps minor, cingulum [mean right and left], and ILF [mean right and left]), including Beck Depression Scale as a covariate since most adolescents met criteria for MDD while all but one adult subject did not.

### 3. Results

See Table 1 for clinical characteristics and self-report instruments scores. Demographic and clinical measures were compared using student’s t test for continuous and Chi-square for categorical variables. Although within age groups (adolescent and adult samples respectively) BPD patients and HCs were matched by age and sex, there were significant differences in the gender distribution of adolescent BPDs compared to adult BPDs (Yates’ chi-square = 12.5; df = 1; p = 0.0004). Adolescent BPDs had a higher proportion of females, while adult BPDs had a higher proportion of males. Therefore, sex was included as a factor in all of the analyses comparing outcome measures across the two age groups. Since most adolescents met criteria for MDD while all but one adult subject did not, we also included Beck Depression Scale as a covariate in the analyses across the two age groups. Because BPD adolescents also differed from BPD adults in aggression scores (BPAQ) and trait Anger (STAXI-T) (See Table 1) we repeated the analyses adding these measures as covariates.

See Table 2 for Axis I diagnoses in adolescent and adult BPDs. See Table 3 for medication list for the adolescent subjects. Adult subjects were not on medication at the time of study. Although adult BPDs were collected in an outpatient setting and adolescent BPDs on an inpatient unit, they did not differ in severity of affective lability, impulsivity, or depression. However, adult BPDs showed more aggression and state anger. Our adolescent sample overlaps with a sample in which we reported regional brain volumes but not DTI (Goodman et al., 2011), in that 10 of the 14 BPD and all the HC subjects were included in that analysis.

t-Tests comparing FA between BPD and HC in the major white matter tracts (i.e. forceps major, forceps minor, left cingulum, right cingulum, left ILF, right ILF) in the adolescent sample showed a tract-specific bilateral decrease in FA in the ILF of BPD adolescents compared to HC adolescents (left ILF t = 3.13, p < 0.005; right ILF t = 2.92, p < 0.008; p > 0.1 for other tracts). See Fig. 1. t-Tests comparing FA between adult BPD and HC in the same major white matter tracts showed no significant group differences.

The mixed factorial repeated measures analysis of variance on FA in an age cohort (adolescent, adult) × group (BPD, HC) × sex (male, female) × tract analysis (forceps major, forceps minor, cingulum [mean right and left], and ILF [mean right and left]) including Beck Depression Scale as a covariate showed that HC adolescents had significantly higher FA in the ILF compared to adolescent BPD and compared to adult BPD and adult HCs (Wilks F(3,52) = 4.74, p < 0.001; post-hoc Fisher LSD: adolescent HC > adult HC (p < 0.001), adolescent HC > adolescent BPD (p < 0.02), adolescent HC > adult BPD (p < 0.05)). There was no significant effect involving sex. See Fig. 2. Because BPD adolescents also differed from BPD adults in aggression scores (BPAQ) and trait Anger (STAXI-T) (See Table 1) we repeated the analysis above adding these measures as covariates. The results were similar with HC adolescents showing significantly higher FA in the ILF compared to adolescent BPD, as well as adult BPD and adult HCs (Wilks

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC (n = 13)</td>
<td>BPD (n = 14)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.2 (9.3)</td>
<td>15.8 (1.1)</td>
</tr>
<tr>
<td>Sex</td>
<td>9F, 4M</td>
<td>12F, 2M ***</td>
</tr>
<tr>
<td>ALS</td>
<td>28.8 (26.1)</td>
<td>92.4 (26.9) #</td>
</tr>
<tr>
<td>BIS-11</td>
<td>74.5 (43)</td>
<td>73.8 (53)</td>
</tr>
<tr>
<td>BPAQ</td>
<td>46.1 (7.6)</td>
<td>52.3 (23.9) **</td>
</tr>
<tr>
<td>BDHI</td>
<td>2.3 (4.2)</td>
<td>20.8 (12.4) #</td>
</tr>
<tr>
<td>STAXI-T</td>
<td>13.9 (3.5)</td>
<td>21.8 (6.5) #</td>
</tr>
</tbody>
</table>

### Table 2

| Axis I comorbidity in BPD groups. |
|---|---|
| | Adolescents | Adults |
| MDD now | 11/14 | 1/24 |
| MDD past | 12/14 | 23/24 |
| Dysthymia | 2/14 | 1/24 |
| OCD | 1/14 | 2/24 |
| Social phobia | 0/14 | 4/24 |
| PTSD now | 2/14 | 4/24 |
| PTSD past | 2/24 | 8/24 |
| ODD | 9/14 | N/A |
| ADHD | 4/14 | N/A |

Table 3 describes current medications for each subject in our adolescent BPD sample. Adult subjects were taking no medications at the time of study.

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate, bupropion</td>
<td>1.</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2.</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>3.</td>
</tr>
<tr>
<td>Aripiprazole, citalopram</td>
<td>4.</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5.</td>
</tr>
<tr>
<td>Citalopram</td>
<td>6.</td>
</tr>
<tr>
<td>Sertraline</td>
<td>7.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>8.</td>
</tr>
<tr>
<td>None</td>
<td>9.</td>
</tr>
<tr>
<td>Fluoxetine, escitalopram</td>
<td>10.</td>
</tr>
<tr>
<td>Escitalopram, amphetamine/dextro-amphetamine, lamotrigine, aripiprazole</td>
<td>11.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>12.</td>
</tr>
<tr>
<td>Sertraline, fluoxetine, risperidone</td>
<td>13.</td>
</tr>
<tr>
<td>None</td>
<td>14.</td>
</tr>
</tbody>
</table>

Table 3 describes current medications for each subject in our adolescent BPD sample. Adult subjects were taking no medications at the time of study.

We examined correlations between FA in forceps major, forceps minor, left and right cingulum, left and right ILF with depression, affective lability, impulsive aggression and trait anger in the adolescent and adult samples separately. No correlations between clinical symptoms and FA in any tract survived correction for multiple comparisons.

4. Discussion

Our principal finding is decreased FA in temporal white matter tracts in adolescents, but not adults, with BPD. Specifically, tractography revealed a robust tract-specific bilateral decrease in ILF FA in BPD adolescents compared to HC adolescents, but no differences between adult BPDs and adult HCs. This finding led us to explore more thoroughly the white matter tracts within temporal lobe in BPD adolescents; voxelwise TBSS analysis demonstrated FA reductions throughout temporal white matter tracts, especially on the left. This analysis revealed FA decreases not only in ILF but also in both uncinate and occipitofrontal fasciculi. Consistent with other studies of BPD adolescents (Rusch et al., 2007), we found no effect of BPD diagnosis on FA in our adult cohort.

ILF FA was significantly higher in adolescent controls compared to BPD adolescents, BPD adults and adult controls. When comparing FA cross-sectionally across the entire lifespan, most white matter tracts demonstrate an inverted U-shaped curve, with FA increasing progressively through adolescence, and leveling off and slowly decreasing in adulthood (Hasan et al., 2010). In parallel to this developmental process, normal brain maturation from childhood to adolescence shows a pattern of increasing synaptogenesis and prefrontal myelination, with subsequent synapse pruning and remodeling (Giedd et al., 2010). Our findings suggest that, in adolescent BPD patients, this normal developmental “peak” in FA, which is seen in healthy controls, is not achieved.

This finding may represent a biological marker for those at risk for the development of BPD. During this developmental window, early intervention preventive and treatment strategies may improve future clinical outcome. Although fronto-temporal white matter connections appear to develop late (Supekar et al., 2010), the ILF normally demonstrates among the earliest and most rapid changes in FA with age, and these changes appear to be consistent with a process of increasing myelination of pre-existing fibers (Lebel et al., 2008).

The consequences of a developmental delay in ILF maturation are not clear. The ILF is a ventral associative bundle connecting visual areas to the amygdala and hippocampus (Catani et al., 2003). Individuals with brain lesions in this area show poor object naming ability (Mandonnet et al., 2007; Shinoura et al., 2010) and difficulty in recognition of facial affect (Philippi et al., 2009), a basic element of social cognition. A profound deficit in the ability to describe feelings and high levels of alexithymia have been reported in adult BPD (Guttman and Laporte, 2002; New et al., 2012). Our finding of low FA in the ILF, a brain region implicated in object naming and emotion recognition, provides an interesting potential neural substrate for this difficulty in naming and describing affect in BPD. We theorize that impaired connectivity in this region during adolescence may be associated with an inability to learn how to adaptively implement basic semantic processing and integrate these functions into higher-order social cognitive processes, a developmental milestone that typically reaches its pinnacle during adolescence. Abnormalities in the ILF may therefore lie at the core of the dysfunctional mentalizing (Tonajy and Luyten, 2009) and representational disturbances (Bender and Skodol, 2007) seen in BPD. ILF connectivity is required for semantic processing (Mandonnet et al., 2007), and the development of semantic processing may thus be a necessary first step for higher-order social cognitive and affective neural processing, which is disturbed in BPD.

Our follow up TBSS analysis revealed decreased FA in other tracts within the temporal lobe, including uncinate and occipitofrontal fasciculi.
occipitofrontal fasciculi. This is especially interesting because it provides evidence for a possible neural substrate for the previously reported OFC-amygdala disconnect seen in adults with BPD (New et al., 2007). This raises the possibility that the structural abnormality in BPD apparently present in adolescence may not be appreciable in adult BPD, but that there remains a functional abnormality in the coordination among brain regions that remains into adulthood. This point is speculative and would require a longitudinal study to adolescent BPD for better empirical grounding, but a similar perspective on volume changes has previously been considered (Brunner et al., 2010; Chanen et al., 2008c).

We note that our tractography finding in ILF is bilateral, whereas the TBSS finding is predominantly in the left hemisphere. Our interpretation of this is that, by nature, voxel-wise statistics have

![Fig. 2. DTI tractography comparing adolescent and adult borderline personality disorder patients: Adolescent patients with BPD showed reduced FA in tractography analysis compared to normally developing adolescents specifically in inferior longitudinal fasciculus in both hemispheres, but no differences in other tracts. Healthy adolescent controls had higher FA in ILF compared to adolescents with BPD, adults with BPD and adult healthy controls (Wilks $F(3,52)=4.74$, $p<0.001$; post-hoc Fisher LSD: adolescent HC > adult HC ($p<0.001$), adolescent HC > adolescent BPD ($p<0.02$), adolescent HC > adult BPD ($p<0.05$)).](image1)

![Fig. 3. TBSS statistical analysis: Adolescent BPD patients showed a reduced FA throughout the temporal lobe (shown in red; $p<0.05$, family wise error corrected for multiple comparisons). FA differences are projected onto the white matter tracts for reference: The uncinate fasciculus in blue, occipitofrontal fasciculus in yellow, and the inferior longitudinal fasciculus in green.](image2)
The Axis I diagnostic comorbidities seen in our sample (and seen ubiquitously in BPD) (Zanarini et al., 2004), prompted us to compare our findings in adolescent BPD with DTI findings in adolescent samples with the Axis I disorders represented in our sample as well as certain prototypic Axis I disorders exemplifying some of the symptoms domains of BPD. Of note, our finding of decreased FA bilaterally in ILF in BPD adolescents is not reported in adolescents with the Axis I disorders most represented in our sample: MDD and ADHD. In adolescent MDD, broad changes in FA have been shown throughout many areas of the brain, including subgenual and supragenual ACC, right and left uncinate, but not ILF (Cullen et al., 2010). Similarly, adolescents at familial risk for MDD showed widespread decreases in FA in cingulum, the splenium of the corpus callosum, the superior longitudinal fasciculi, uncinate and fronto-occipital fasciculi (Huang et al., 2011). DTI studies in ADHD adolescents have been inconsistent. Most, like in MDD, have shown broad decreases in FA, in regions including superior longitudinal fasciculus (including arcuate fasciculus) (Hamilton et al., 2008), frontoparietal and frontolimbic, and temporoparietal areas (Nagel et al., 2011), anterior limb and superior regions of the internal capsule and anterior corona radiata (Pavuluri et al., 2009). Other studies have shown increased FA in ADHD, in tracts including parts of the cingulum, uncinate, superior and inferior longitudinal fasciculi (Silk et al., 2009) and anterior corona radiata (Davenport et al.). While there are inconsistencies in DTI findings in ADHD, it seems unlikely that our findings are the result of comorbid ADHD because we have only few subjects with co-morbid ADHD and FA in ILF in ADHD adolescents, if different from healthy controls, appears to be increased (Silk et al., 2009).

One disorder in which decreased FA in ILF has been reported is schizophrenia. Adult schizophrenic patients and their first-degree relatives show decreased FA in the ILF (Cheung et al., 2008; Clark et al.), with negative correlations between FA and positive psychotic symptoms (Mitelman et al., 2007). Similarly, children and adolescents with schizophrenia (Ashari et al., 2007) and subclinical psychosis (Jacobson et al., 2010) demonstrate a similar association between ILF FA and positive psychotic symptoms, with one study indicating the prognostic significance of this white matter abnormality for future social functioning (Karlsodt et al., 2009). Another diagnosis associated with decreased white matter integrity in ILF is autism, both in adults (Thomas et al., 2011) and adolescents (Jou et al., 2011; Pugliese et al., 2009). Of note, none of our adolescent subjects had a diagnosis of schizophrenia, current psychosis or autism.

Comparing our DTI results to those found in bipolar affective disorder (BD), a disorder like BPD of severe mood instability, showed some similarities but also some differences. Adults with BD (Bruno et al., 2008) and those considered genetically “at-risk” (Chaddock et al., 2009) demonstrated lower FA in the ILF, although others failed to demonstrate any ILF abnormality in bipolar children (Barnea-Goraly et al., 2009; Pavuluri et al., 2009). In a cross-sectional study, healthy offspring of bipolar patients showed lower ILF FA than healthy offspring of healthy individuals (Versace et al., 2010). There is a shared familial risk for BD and BPD (Gunderson et al., 2006) although our current sample excludes those with bipolar I. Thus, similar changes in ILF have been found in schizophrenia, BD, and autism; however, DTI findings in children and adolescents have usually been similar to those seen in adults. By contrast, in BPD, differences in ILF connectivity appear to be evident in borderline adolescents and not adults. Future studies following subjects longitudinally would be helpful to track the course of illness of individuals with affective instability and their white matter FA over time to explore emergent diagnoses.

The primary limitation of this study is its cross-sectional nature. Because we are comparing two separate adult and adolescent populations, the possibility remains for an inadvertent sampling bias between the two age cohorts. Specifically, the sample of adolescents included mostly subjects on psychotropic medication at the time of the DTI imaging while the adult sample was unmedicated. While it remains possible that the differences in FA in the ILF that we find between adolescents with BPD and healthy adolescents may be accounted for by medication and this is a limitation of our study, we believe this to be unlikely. Somewhat surprisingly, evidence suggests that psychotropic medication may have a larger effect on structural MRI than on functional MRI or on DTI outcomes (Hafeman et al., 2012). Indeed, this recent review on the effect of psychotropic medication on brain imaging in bipolar disorder found a minimal effect on DTI results. Furthermore, the effect of medication on structural imaging was to normalize the abnormal structural findings in bipolar disorder to resemble unaffected controls (Hafeman et al., 2012). The implication of this for our data would tend to suggest that, if anything, the presence of current psychotropic medications in our BPD adolescents might diminish the differences compared to healthy adolescents; in contrast, we would expect the unmedicated BPD adults to retain any abnormal brain imaging finding. Our data show just the opposite, perhaps suggesting that the differences between BPD adolescents and healthy controls would be even larger if BPD adolescents had been unmedicated. While we acknowledge that we cannot definitively comment on this in our sample, we do note that recent DTI research in schizophrenia, autism, bipolar disorder, and non-clinical samples has utilized a similar cross-sectional strategy, likely in an effort to identify regions of interest for future, prospective developmental research.

A similar and important limitation involves differences between our adolescent and adult samples: adolescents were recruited from an inpatient population and met criteria for MDD,
show that even with more limited resolution, akin to the interpolation done when there is a gap, tractography is still highly robust when multiple anatomical criteria are stipulated (Huang et al., 2004; Wakana et al., 2007).

Future prospective research in adolescents will clarify whether abnormalities in temporal lobe white matter are a measurable biomarker of risk for BPD. If so, future research will also assist in determining the nature of early intervention to prevent future onset of BPD or mitigate its severity. Our results suggest that the course of BPD across the lifespan may involve a specific neurobiological abnormality in ILF, perhaps related to semantic processing of affect, during a specific developmental window. Our findings call for attention to developmental changes in affective and social cognitive neurobiology in BPD. By identifying individuals at-risk with a neurobiological marker, we can increase our understanding of the fundamental psychopathology of BPD, as well as develop psychotherapeutic and psychopharmacologic strategies for prevention and clinical improvement.

Financial disclosure and conflict of interest


Contributors

Marianne Goodman, Erin A. Hazlett and Antonia S. New conceived the idea for the study. David M. Carpenter and Erin A. Hazlett conducted the image processing and statistical analysis of the MRI data. Antonia S. New, Luis H. Ripoll, M. Mercedes Perez-Rodriguez, Jennifer Avedon, Uday Patil contributed to the statistical analyses. Luis H. Ripoll, Antonia S. New and M. Mercedes Perez-Rodriguez managed the literature searches. Antonia S. New and M. Mercedes Perez-Rodriguez wrote the first draft of the manuscript. Marianne Goodman, David M. Carpenter, Luis H. Ripoll, M. Mercedes Perez-Rodriguez, Jennifer Avedon, Uday Patil, and Erin A. Hazlett critically reviewed the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding sources

This work was supported by a VA Career Development grant to MG and by grants from the National Institutes of Health (NIH) to ASN (1-R01-MH067918-01) and to EAH (R01MH073911) and by 5-M01 RR00071 for the Mount Sinai General Clinical Research Center from the National Center for Research Resources at the NIH. MMPR is supported by the Department of Veterans Affairs Office of Academic Affiliations Advanced Fellowship Program in Mental Illness Research and Treatment, the Medical Research Service of the Veterans Affairs James J Peters VAMC, and the Department of Veterans Affairs NY/NJ (VISN3) Mental Illness Research, Education, and Clinical Center (MIRECC).

Acknowledgments

This research is supported by the Department of Veterans Affairs Office of Academic Affiliations Advanced Fellowship Program in Mental Illness Research and Treatment, the Medical Research Service of the Veterans Affairs James J Peters VAMC, and the Department of Veterans Affairs NY/NJ (VISN3) Mental Illness Research, Education, and Clinical Center (MIRECC).
References


